REMARKS

Claim 23 has been canceled. New claim 39 has been added. Claims 1-13, 15, 38, and 39 are currently pending in the application. Claims 1-7 have been amended according to the elected invention. Claims 1-6 and 9-10 have been amended in response to the Examiner's written description rejection. Support for these amendments can be found throughout the application and the original claims, e.g., at paragraphs [0004]-[0005], [0048], [0087], [0137], and [0140]-[0145], and original claims 22 and 23. Consequently, no new matter has been added by the way of these amendments. Consideration of the amendments and remarks herein is respectfully requested.

I. Rejections based on 35 U.S.C. § 112, first paragraph

Claims 1-13, 15, 23, and 38 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1-13, 15, 23, and 38 also stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enablement for the full scope of the claims. As noted above, claim 23 has been canceled. These rejections are respectfully traversed.

1. Written Description of "IL-21R"

Possession of the Invention

The Examiner argues that the claims fail to comply with the written description requirement because the specification allegedly does not adequately describe the term "IL-21 receptor" used in the claims (see *Office Action*, page 2, line 15 - page 5, line 17). The Examiner cites six portions of the specification to construe the phrase "IL-21 receptor," and contends that

because the specification presents a variety of alternative definitions, one skilled in the art would not be able to envision the IL-21 receptor as a claim limitation (see *Office Action*, pages 3-4).

The purpose of the written description requirement is to ensure that the applicant possessed the claimed invention at the time of the filing. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002). For chemical compounds such as genes or proteins, an applicant must disclose sufficient identifying characteristics so one of skill can "visualize or recognize the identity" of the invention. *Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). For a generic claim, the specification must describe "species sufficient to constitute the genera." *Enzo*, 323 F.3d at 967. The MPEP §2163 states that addressing the written description requirement for a genus requires the analysis of several factors.

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the methods of making the claimed invention. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The present invention describes specific antibodies raised against IL-21 receptor ("IL-21R"). The specification presents two exemplary sequences of the IL-21R, mouse IL-21R, represented by SEQ ID NO:45, and human IL-21R, represented by SEQ ID NO:43 (see *Specification*, at [0048]). The IL-21R is capable of binding an IL-21 cytokine ligand, and the binding of ligand to the receptor initiates a number of immune processes.

The Examiner contends that the claims do not satisfy the written description requirement because description of only human and mouse IL-21R is allegedly insufficient to

describe the genus of IL-21R (see *Office Action*, page 5, lines 13-17). Applicants have amended the claims to recite that the antibodies must bind to a polypeptide with at least 85% identity to either human (SEQ ID NO:43) or mouse (SEQ ID NO:45) IL-21R, or a fragment thereof, with the requirement that the IL-21R or fragment thereof is capable of binding the IL-21 ligand. Thus, as amended, the claims recite a sequence, species, and functionality. Applicants submit that in light of the present amendments, the polypeptide that the antibodies of the invention are capable of binding is sufficiently described in the specification.

Applicants also submit that one of ordinary skill in the art would recognize that the inventors were in possession of the genus of IL-21Rs recited in the amended claims, i.e., receptors with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the receptor is capable of binding IL-21. Applicants have adequately described the physical, structural, and functional properties of a genus of polypeptides with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the polypeptides in the genus are capable of binding IL-21. In the instant claims, Applicants specify that the polypeptide is capable of binding the IL-21 ligand. At the time of filing, one skilled in the art would recognize, based on the disclosed IL-21R sequences and the knowledge available in the field regarding cytokine receptor-ligand interactions, that alignment of the IL-21R sequences from different species (e.g., mouse and human) and the alignment of IL-21R with other interleukin receptors (e.g., IL-2) would indicate regions of the IL-21R responsible for ligand binding.

Published International Application WO 01/85792 (previously submitted as part of an Information Disclosure Statement (IDS); a courtesy copy is provided herewith), which is

incorporated by reference in the present application at [0005], presents an alignment of mouse and human IL-21R with a homologous IL-2 receptor (see Figure 5 of WO 01/85792). One of skill in the art could use this alignment, for example, to identify IL-21Rs within the scope of the instant claims, and thus would recognize that Applicants possessed the recited genus. In addition, numerous other references available at the time of filing discussed specific domains and residues in hematopoietic receptors that are important for ligand binding and receptor signaling[1] (see, e.g., Woodcock et al. (1994) *EMBO J.* 13:5176-85; Mulhern et al. (2000) *J. Mol. Biol.* 297:989-1001; Schimmenti et al. (1995) *Exp. Hematol.* 23:1341-46; LaRosa et al. (1992) *J. Biol. Chem.* 267:25402-06; Imler et al. *EMBO J.* 11:2047-53 (submitted herewith as part of an IDS); Bazan (1990) *Proc. Natl. Acad. Sci. USA* 87:6934-38) (previously submitted as part of an IDS; a courtesy copy is provided herewith)). Therefore, Applicants respectfully submit that one skilled in the art would recognize that they possessed a genus of (IL-21R) polypeptides with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the polypeptides in the genus are capable of binding IL-21.

In addition, other physical / chemical and structural properties of IL-21Rs are known in the art. For example, WO 01/85792 discloses the position of conserved domains of the IL-21R (e.g., WSXWS motifs, Box 1 and Box 2 signaling motifs, potential STAT docking sites, etc.), its leader sequence, and transmembrane domains (see Figures 2 and 5, Example 2, and page 9, lines 7-23 of WO 01/85792); further, the present application teaches the extracellular domain of IL-21R (see *Specification*, [0075]). Therefore, a skilled artisan would know which regions of

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[1]A specification "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

the IL-21R are important for its various biological activities, and with this information would recognize that Applicants disclosed species of IL-21R sufficient to demonstrate possession of the recited IL-21R genus.

Applicants also describe functional properties of the IL-21R genus. For instance, the specification states that IL-21R function may include modulation of T cells, NK cells, B cells, macrophages, and synovial cells (see *Specification,* [0006]). The specification also indicates IL-21R involvement in progression of immune disorders, e.g., arthritis and transplant rejection (see *Specification*, Examples 12-13). As these functions are mediated by the IL-21 ligand binding to the IL-21R, and binding is explicitly noted as a claim limitation in the amended claims, Applicants have functionally characterized the recited genus.

Applicants respectfully submit that given the level of knowledge in the art of cytokine receptors, and the chemical, structural and functional properties of IL-21R described in the specification, Applicants have adequately described a genus of polypeptides with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the polypeptides in the genus are capable of binding IL-21. For at least these reasons, Applicants respectfully request withdrawal of the written description-based rejection of the claims.

Reduction to Practice

The Examiner also contends that Applicants have not shown reduction to practice, and therefore allegedly have not achieved conception of IL-21R polypeptides other than the mouse and human IL-21Rs. Applicants respectfully disagree.

> [A]ctual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps.

(See *Guidelines for Examination of Patent Applications under the 35 U.S.C. §112, ¶1, "Written Description" Requirement,* 66 Fed. Reg. 1099-1111, 1101). For the reasons discussed above, Applicants respectfully submit that they have described chemical, structural, and functional properties of polypeptides with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the polypeptides are capable of binding IL-21; as further noted, other properties of such polypeptides are known in the art (see, e.g., WO 01/85792). In addition, previous publications clearly describe how to make IL-21R species (see WO 01/85792, Example 1; primers based on human IL-21R sequence were used to amplify a 300 nucleotide stretch of mouse IL–21R, and primers derived from the 300 nucleotide stretch were used to screen a mouse cDNA library to identify the full length mouse IL-21R clone). Thus, Applicants submit that this is not a rare instance that requires one to actually reduce the recited genus to practice.

Further, Applicants submit that they have shown conception of the IL-21R genus recited as a claim limitation. Conception of a chemical compound occurs if an inventor "has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). Applicants, either directly or by reference, have shown conception by disclosing the characteristics of the IL-21R

genus, have defined the genus by indicating physical / chemical, structural, and functional properties of genus members, and have disclosed methods of producing species within the IL-21R genus. Therefore, Applicants respectfully submit that they have provided evidence of conception of the scope of the claims, and accordingly have shown possession of the claimed invention. For at least these reasons, Applicants respectfully request withdrawal of the written description-based rejection of the claims.

2. Written Description of the Antibody

The Examiner alleges that the definition of the antibody given in the specification, namely that an antibody is an immunoglobulin or fragment thereof that "'encompasses any polypeptide comprising the antigen binging site'... where an antigen binding domain could be an isolated complementarity determining region (CDR)" contradicts teachings of the art (see *Office Action*, page 5, line 18 - page 6, line 4). According to the Examiner, antibody specificity requires at least five, if not six CDRs (*id.*).

Applicants respectfully disagree. It is well known in the art that antigen recognition does not require a minimum of five CDRs. For instance, as indicated at [0042-0043], single domain antibodies (dAbs) can be functional. Single domain antibodies contain three CDRs. Ward et al. teach that isolated VH domains with good antigen binding affinities can be prepared (cited at [0043] of the specification; (1989) *Nature* 341:544-46) (previously submitted as part of an IDS; a courtesy copy is provided herewith). These VH domains contain three CDRs. Such antibodies also exist in nature; particularly, it is known that camels and llamas have developed non-VL domain-containing antibodies as a part of their humoral response

system. [For an extended review, see Muyldermans (2001) *Rev. Mol. Biotechnol.* 74:277-302; see also Muyldermans et al (2001) *Trends Biochem. Sci.* 26:230-35 (both submitted herewith as part of an IDS).] These dromedary antibodies contain three CDRs. Van den Beucken et al. teach the use of single VL domains as protein binding molecules ((2001) *J. Mol. Biol.* 310:591-601) (submitted herewith as part of an IDS). These single VL domains contain three CDRs. Hence, Applicants submit that it is well known in the art that a functional antibody can consist of less than five CDRs. Therefore, Applicants submit that the disclosed description of an antibody does not contravene the accepted state of art at the time of filing. For at least this reason, Applicants respectfully request withdrawal of this written description-based rejection.

3. Enablement Rejection

The Examiner rejected claims 1-13, 15, 23, and 38 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement for the full scope of the claims. For the following reasons, that rejection is respectfully traversed.

The Examiner alleges that the IL-21R protein is so broadly described in the specification, that one skilled in the art would not be able to use any antibody that is not described in the examples. As discussed above in the written description section, the IL-21R genus is not overly broad, and one of skill in the art would not be prevented from making the genus of antibodies described. Applicants claim antibodies that selectively bind to a polypeptide with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof. Thus, the antibodies of the invention, including the antibodies with substituted CDRs, must bind IL-21R. As indicated in the specification, the antibodies of the invention are

useful in diagnosing, preventing, and/or treating immune disorders. Applicants submit that a skilled artisan would know from the specification how to use the antibodies of the invention.

The Examiner also alleges that one skilled in the art would not know how to make antibodies of the invention. Applicants respectfully disagree. To satisfy 35 U.S.C. § 112, an applicant must disclose an amount sufficient to allow one skilled in the art to practice the invention without undue experimentation (see *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991)). However, that some experimentation (or even extensive experimentation) is required to practice a claimed invention does not necessarily invalidate a claim under § 112 (see *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (stating "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.")). Therefore, "[e]nablement is not precluded by the necessity for some experimentation . . . . 'The key word is 'undue,' not 'experimentation.'" *In re Wands*, 858 F.2d at 736-7 (quoting, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974)). Accordingly, trial-and-error may be acceptable and will not render a claim invalid if the experimentation is routine or the specification provides a reasonable amount of guidance (see *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal . . . .")).

Applicants submit that one skilled in the art would know how to make useful antibodies that bind to the IL-21R genus recited in the claims, as well as the antibodies having one or more mutated CDRs. First, as WO 01/85792, Example 1, demonstrates, one skilled in the art would know how to make IL-21R of various species. This does not require undue experimentation. Additionally, one skilled in the art would also know how to introduce changes

into these IL-21Rs, e.g., amino acid deletions, substitutions, etc. (see "Site Directed Mutagenesis" § 20-3 (pp. 738-44) in Basic Methods in Molecular Biology, 2nd Edition (1994) Davis et al. (Eds.) Appleton & Lange, CT) (submitted herewith as part of an IDS). This does not require undue experimentation. One skilled in the art would also know how to test whether these IL-21R species bind an IL-21 ligand (e.g., by using a well-known ELISA assay). This does not require undue experimentation. In addition, methods of making antibodies, e.g., to IL-21R, are routine in the art (see *Specification*, at [0062]). This also does not require undue experimentation. Thus, Applicants submit that any experimentation required to generate IL-21R species, test whether the species bind IL-21, and make antibodies against these IL-21Rs is not undue, and involves merely routine trial and error.

The Examiner also contends that the specification does not enable the full scope of the claims because one skilled in the art would be unable to predict whether antibodies with "conservative" substitutions (as referred to in claims 4 and 5) will still bind antigen. However, claims 4 and 5 only refer to antibodies with conservative substitutions, wherein such substitutions do not produce an antibody that fails to bind IL-21R. Thus, any antibodies that cannot bind to IL-21R are excluded from the scope of the claims. Exemplary conservative substitutions are demonstrated in Table 3 of the specification, and described in the specification at [0081]-[0084]. Introducing conservative and nonconservative substitutions is routine in the art, e.g., using site-directed mutagenesis (see, "Site Directed Mutagenesis," *supra*). This does not require undue experimentation. The methods of determining whether a mutated antibody binds to the receptor are also well known in the art, e.g., the ELISA-based technique described in Example 5 of the specification. This also does not require undue experimentation. Therefore,

using well-known routine methods and the teachings of the specification, one skilled in the art could easily introduce conservative substitutions into an antibody of the invention and determine whether the antibody or fragment thereof retains its ability to bind to IL-21R. Thus, Applicants submit that not a single step of the process used to make antibodies with modified CDRs requires anything more than routine trial and error, and, thus, none of the steps as a whole require undue experimentation.

For at least these several reasons, Applicants respectfully request withdrawal of the enablement-based rejection of the claims.

II. Rejections based on 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-13, 15, 23, and 38 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter of the invention.

The Examiner states that because the claims have, as a defining characteristic, binding to IL-21R, and because such receptor is allegedly not adequately described, the claims are indefinite, i.e., because the antibody cannot be envisioned without the antigen (see *Office Action*, page 7, line 19 – page 8, line 3). In view of the amended claims and Applicants' remarks regarding the adequacy of the description of a genus of polypeptides with at least 85% identity to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45, or a fragment thereof, wherein the polypeptides in the genus are capable of binding IL-21, Applicants submit that the Examiner's indefiniteness-based rejection has been similarly overcome. For at least this reason, Applicants respectfully request withdrawal of the indefiniteness-based rejection of the claims.

The Examiner also contends that the phrase "conservative substitution thereof" in claims 4 and 5 renders the metes and bounds of these claims indefinite. For the following reasons, that rejection is respectfully traversed.

Claim language need only "reasonably apprise those skilled in the art of the utilization and scope of the invention." *Shatterproof Glass Corp. v. Libbey-Owens Ford, Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985). An applicant is not required to use the best or most well-known term to describe a particular element; rather the test for indefiniteness is whether or not those skilled in the art would understand the scope of a claim when the claim is read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). The specification describes the term "conservative amino acid substitution" as a substitution of a native amino acid with a nonnative amino acid "such that there is little or no effect on the polarity or charge of the amino acid residue at that position" (see *Specification*, at [0082]). In addition, the specification teaches that "[c]onserved modifications will produce molecules having functional and chemical characteristics similar to those of the molecule from which such modifications are made" (*id.*, at [0081]). The specification also presents exemplary conservative substitutions in Table 3 (at page 36). Because the specification describes and exemplifies conservative amino acid substitutions, and because the claims require an antibody containing a substitution in a CDR to bind to a polypeptide at least 85% identical to the polypeptide set forth in SEQ ID NO:43 or SEQ ID NO:45 or a fragment thereof, Applicants submit that those skilled in the art would understand the scope of the claims when read in light of the specification. Therefore, Applicants respectfully request withdrawal of the indefiniteness-based rejection of claims 4 and 5.

The Examiner also rejects claims 15 and 38 as incomplete because both the pharmaceutical composition and the kit allegedly must comprise at least two elements. Claims 15 and 38 have been amended to contain at least two elements, and support for these amendments may be found at [0137] and [0140]-[0145], respectively. In light of these claim amendments, Applicants request the withdrawal of the indefiniteness-based rejections of claims 15 and 38.

III. Rejection based on 35 U.S.C. § 102(b)

The Examiner has rejected claims 4, 5, 8-13, 15 and 38 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C.§ 103(a) as obvious over WO 00/069880 ("Hodge"). The Examiner alleges that Hodge claims an antibody that selectively binds to human IL-21R. The Examiner contends that although Hodge does not disclose any CDR sequences of the antibody, because antibody specificity is conferred by CDR regions, an antibody of Hodge would have contained at least a number of CDRs enumerated in the instant application (see *Office Action*, pages 8-9). For the following reasons, that rejection is respectfully traversed.

In order to invalidate a claim as anticipated, an Examiner must establish that each and every element of that claim is present in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Mere probability is insufficient to establish inherency. *Id.* Thus, the Examiner has a burden of proving that the antibodies present in Hodge necessarily contain the CDR sequences recited in the pending claims.

In light of the absence of sequence disclosure in Hodge, Applicants submit that the Examiner has not established that antibodies with the same sequences as those of the present

invention were necessarily present in Hodge. Therefore, the Examiner has not carried the burden of proving that every element of claims 4, 5, 8-13, 15, and 38 is present in Hodge. For at least this reason, Applicants respectfully request withdrawal of the outstanding anticipation-based rejection of claims 4, 5, 8-13, 15, and 38.

Applicants also submit that disclosure of a genus of IL-21R antibodies in Hodge does not make specific antibodies disclosed in the present application obvious. The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 389, 382, 20 USPQ2d 1550, 1552 (Fed. Cir. 1994). To establish *prima facie* obviousness in a genus-species chemical compound situation, the Examiner must identify some motivation or suggestion to make the claimed invention in light of the prior art teachings (see *In re Brower*, 77 F.3d, 422, 425 (Fed. Cir. 1996)). DNA sequences are chemical compounds, albeit complex ones. *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207 (Fed. Cir. 1991). Thus, to make specific DNA sequences obvious, the cited art (i.e., Hodge) must teach some motivation to select the specific polynucleotide sequences. *In re Deuel*, 51 F.3d 1552, 1558-59 (Fed. Cir. 1995). Further, because protein sequences (e.g., antibodies), like genes, are chemical compounds, the rules for obviousness in chemical compound cases logically apply to the protein sequences recited in the instant claims. As Hodge cannot possibly inherently anticipate the instant claims, to invalidate the claims as obvious, the Examiner carries the burden of showing that the prior art suggests the claimed antibody sequences. (see *In re Bell* 991 F.2d 781. 784 (Fed. Cir. 1993)). However, Hodge contains no single indication that one skilled in the art should make or select antibodies of the specific DNA and protein sequences recited in the instant claims. Indeed, Applicants submit

that Hodge does not suggest any sequence for any antibody. In light of the lack of disclosure in Hodge of any sequence, less some motivation to select or make the sequences recited in the pending claims, Applicants submit that the Examiner has not established a *prima facie* case of obviousness.

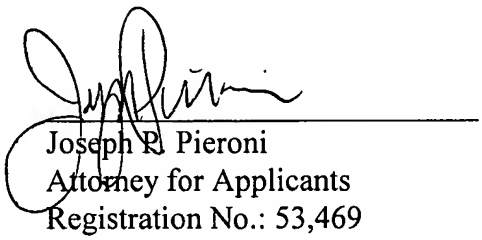
Accordingly, Applicants respectfully request withdrawal of the obviousness-based rejection of claims 4, 5, 8-13, 15 and 38.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns have been answered and overcome, and that the presently claimed invention satisfies 35 U.S.C. §112 and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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